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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,331	12/18/2001	Andrew A. Young	030639.0031,UTL1	2765

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EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1653	22

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,331	YOUNG ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *29 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The response filed 29 April 2003 (Paper No. 21) as to amendment of claims 1, 4-7 and 9-11 and addition of new claims 14-20 have been entered. The following Office action is applicable to the pending claims 1-20.

Note that the grounds of objection and/or rejection not explicitly stated and/or set forth below are withdrawn, and that the text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim/Objections

The disclosure is objected to because of the following informalities:

Claim 8 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only, i.e., cannot depend from any other multiple dependent claim, it is claim 7 herein. See MPEP § 608.01(n). Accordingly, claim 8 has not been further treated on the merits.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for conjugating PEG polymer to exendin-4 peptide and use of the exendin peptide (non-conjugated) for decreasing glucagon secretion in a patient having glucagonoma or Type II diabetes, does not reasonably provide enablement for using the a polymer-modified exendin conjugates to decrease glucagon level in the patient thereof. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant application does not provide working example, a description as to treatment of the disorders glucagonoma and glucagonoma-related necrolytic migratory erythema (see Bloom, S. R. *et al.* (1987) *Am. J. Med.* 82, (suppl 5B) 25-36), which are characterized by abnormally high blood glucagon levels, via administering to patients a pharmaceutical composition comprising a polymer-modified exendin or analog thereof.

The application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The nature of the invention:

The claims as written are directed to use of a polymer-modified exendin or analog thereof as a pharmaceutics to treat the diseases, e.g., the glucagonoma and type II diabetes. The specification establishes the method of preparation exendin and the PEG-modified exendin peptides, shows a decrease of plasma glucagon mediated by exendin-4 peptides, the effect of the

peptide on glucagon secretion in patients with glucagonoma or type II diabetes (see claims 12-13). However, the specification is silent as to use of a polymer-modified exendin to lower glucagon level and treat the disease thereof.

The specification only describes PEG-modified exendin-4 and its cellular clearance by the kidney (Example 6). Yet, the specification does not provide working examples and guidance as to polymer-modified exendin and analogs thereof. One of skill in the art would not know whether the polymer moiety in the modified exendin include any chemical polymer compound or biopolymer molecules, and, whether the exendin analog encompasses any structural or/and functional derivative, e.g., GLP-1 which has the same effect as exendin-4 on decreasing glucagon level. Thus, the exendin analog represents a genus encompassing a large number of variants which structures are divergent from unmodified exendin-4. Upon the analog modification by PEG polymer, the activity and therapeutic efficacy of the PEG-modified exendin analog is highly unpredictable, absent the factual indicia to the contrary.

(2) The scope of the claims:

The polymer moiety in a polymer-modified exendin has not been described in the specification; thus, "a polymer" encompasses (i) chemical polymer (*e.g.*, polyol ester), and (ii) biopolymer (*e.g.*, polynucleotide, peptide nucleic acid, polypeptide and lipid). The specification provides no working examples and guidance as to the polymer-modified exendin, e.g., fatty acid modified exendin, nor description of biological activity and therapeutic use of the polymer-modified exendin or analog thereof. In comparison of the limitation set forth by the claims with the disclosure set firth by the specification, the scope of claims is so broad that the scope of

claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

(3) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Because, as above-mentioned, the combination number of the conjugates, i.e., a polymer-modified exendin or analog thereof as claimed are vast and the conjugates are highly variant, and because each variant conjugate has different/distinct water-solubility (see page 10, lines 1-14) that determines pharmaceutical efficacy of the polymer-exendin applicable to the disorders or diseases, absent factual indicia to the contrary, the skilled artisan has to perform undue experimentation in order to screen, test and characterize each conjugate variant, including solubility, biological stability (related to clearance by the kidney (see Example 3)) as well as pharmaceutical efficacy.

On the other hand, different disorders and diseases require different therapeutic procedures and protocols as well as doses and forms of pharmaceutics. Even for treatment of a given disorder, parameters, e.g., dose and administering time for achieving reasonable therapeutic effect of the exendin peptide is needed to be determined (see the bell curves of dose-dependent [Figure 4(d)] and plasma concentration-dependent anti-diabetic effect of the exendin [Figure 4(f)], as well as time-dependent fashion [figure 4(b)] (see Parkes, D. G. et al. (2001) *Metabolism* 50, 583-589). Since the above-mentioned therapeutic parameters are the modified exendin dependent, the specification needs to provide sufficient guidance to support the enablement.

(4) The unpredictability of the art:

Because the claimed method involves highly variant polymer-modified exendin conjugates which is the subject matter of the current invention, outcome of administering the composition comprising the polymer-modified exendin to a subject suffering from glucagonoma or type II diabetes is unpredictable in the absence of factual indicia to the contrary.

(5) The quantity of experimentation necessary:

In the absence of working examples as to the polymer-modified exendin variants and the undetermined therapeutic parameters referring to each variant, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. Because of the reasons forgoing, the quantity of experimentation would be large and of unpredictability. The skilled artisan would be required to carry out a large quantity of search for water soluble as well as biologically stable polymer-modified exendin variant(s), and to establish a suitable animal model so as to determine therapeutic parameters for treatment of the disorders. For the instance, biological half-life of the antidiabetic composition needs to be determined prior to administering the composition; the clinical utility and development of the antidiabetic composition has been frustrated, at least in part, by its short half-life in man and the need for continuous or frequent administration (see Figure 4(f), pages 583 and 586, Parkes *et al.*).

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to unpredictable polymer-exendin variants. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a protein-engineer, an endocrinologist and a cell biologist at Ph.D. level with several years of experience in peptide

chemistry as well as knowledge in peptide synthesis, organic synthesis, polymer chemistry, endocrinology, oncology, and molecular biology. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable.

One of key parameters affecting the exendin therapeutic effect is the biological half-time *in vivo*. Drucker D. J. *et al.* (*Diabetes* (1998) 47, 159-169) teach that novel glucagon-like peptides, *i.e.*, exendin peptides, are more potent than native glucagon-like peptide 1 (GLP-1) and have higher biological stability than GLP-1 in view of therapeutic application (see the left column of page 164 and the second paragraph). This does not, however, necessarily reflect a polymer-modified exendin or analog thereof is soluble and effective comparable to the unmodified exendin-4 peptide and stable enough being resistant to proteolysis during administration. This is evidenced by the Parkes *et al.* who demonstrate that plasma concentration (as to stability) of exendin peptide is highly dependent upon time and mean of administering (see Figure 4(a) and 4(d)).

The specification describes biological half-time related "clearance by the kidney" of the unmodified exendin-4 peptide (see example 3,and Figures 5 and 6). However, the specification fails to teach the same with regard to the polymer-modified exendin and analog thereof.

In light of the above-mentioned polymer-modified exendin variants, unpredictability of biological half-life and *solubility* of the variants when administered, pre-determination of several therapeutic parameters, *e.g.*, does, time, mean of administering, there is undue experimentation because of variableness in prediction of outcome that is not addressed by the instant application teaching, examples and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

The response to the rejection under 35 USC 112, the first paragraph

The response filed 29 April 2003 argues that applicant has provided considerable direction working examples and guidance for the claimed invention such that it is well within the level of ordinary skill in the art to practice the invention without undue experimentation, and argues against unpredictability of using the polymer-modified exendin and analog thereof for (see page 8). The applicant's argument is found unpersuasive because of the reasons set forth in the previous Office action and the statement *supra*. The application only provides examples for exendin-4 clearance by the kidney (Example 3) and use of exendin-4 in decreasing glucagon secretion in diabetic fatty zucker rats and in patients with type II diabetes (see examples 4-5). The specification does not provide working example and guidance as to biological activity of the modified exendin analog, which encompasses a large number of exendin variants, and as to their increases solubility, resistance to proteolysis (related to biological half-time in vivo) and reduced toxicity. Thus, therapeutic role of the claimed modified exendin analog is unpredictable and undue experimentation is necessary for assessing use of the polymer-modified exendin and analog thereof in treatment of disease states, e.g., glucagonoma and Type II diabetes.

The response asserts that example 6 provides guidance regarding the designing polymer-modified exendin compound and retaining therapeutic activity thereof, e.g., the compound is a glucagonostatic agent for treating glucagonoma and necrolytic migratory erythema, and asserts that the present application yields a predictable result by providing guidance as to the design and selection of the polymer-modified exendin compound and the demonstration of glucagonostatic activity of the compound (see pages 91-10). The applicant's argument is not persuasive. As

stated above, the polymer moiety in a polymer-modified exendin encompasses chemical polymer and biopolymer, e.g., polynucleotide, peptide nucleic acid, polypeptide and lipid etc. The specification provides no working examples and guidance in this regard. Example 6 sets forth clearance of unmodified exendin-4 peptide by the kidney, PEG modification of *exendin-4* and postulate that the polymer-modified exendin would have improved (increased) half-time in vivo. However, the example does not teach any polymer-modification of exendin analog for which the specification provides insufficient description. Moreover the specification does not provide representative working example(s) as to the glucagonostatic activity of the claimed polymer-modified exendin and the activity of exendin analog that is subject to the claimed polymer-modification. Unpredictable bioactivity of the polymer-modified exendin or analog thereof in addition to their therapeutic parameters, e.g., solubility, cellular half-time (i.e., biological stability) and cytotoxicity are highly unpredictable, therefore, has resulted in the necessity of undue experimentation. See also the above rejection.

Claim Rejections - 35 USC § 112

This is a now ground of the rejection due to applicant's amendment which necessitated the rejection presented herein.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification while being enabling for enabling conjugating PEG polymer to the claimed exendin-4 peptide and use of the peptides thereof and unmodified exendin-4 for decreasing glucagon secretion in a patient having Type 2 diabetes, does not reasonably provide enablement for using the *a polymer-modified* exendin conjugates to treat glucagonoma and glucagonoma associated necrolytic migratory erythema and Type II diabetes

Applicant is in possession of the unmodified exendin-4 for decreasing glucagon levels in a patient suffering from disease, e.g., glucagonoma, and PEG-modification of exendin-4. Applicant is not in possession of any polymer-modified exendin molecules, any exendin analogs and any polymer-modified exendin analog compounds, and not in a possession of a method of lowering plasma glucagon in a subject comprising administering the polymer-modified exendin or polymer-modified exendin analog to said subject to treat glucagonoma, glucagonoma associated necrolytic migratory erythema, or Type II diabetes. The current claim language thus encompasses a vast number of the polymer-modified exendin compounds and analogs thereof that are not described in the current application.

The instant application provides no guidance and working examples as to structural and functional characterization of the variants, i.e., any polymer-modified exendin a molecule, any exendin analog and any polymer-modified exendin analog. The polymer moiety in a polymer-modified exendin has not been described in the specification; thus, a polymer encompasses (i) chemical polymer (*e.g.*, polyol ester), and biopolymer (*e.g.*, polynucleotide, peptide nucleic acid, polypeptide and lipid). The specification provides no guidance as to how to make and use the

polymer-modified exendin, e.g., fatty acid modified exendin, nor teaching and direction as to biological activity and therapeutic use of the polymer-modified exendin or analog thereof.

The combination number of the conjugates, i.e., a polymer-modified exendin analog as claimed is vast and highly variant. Because each variant conjugate has different/distinct water-solubility that determines pharmaceutical efficacy of the polymer-exendin applicable to the disorders or diseases, one of skilled artisan would be required to perform undue experimentation in order to screen, test for and characterize one of each conjugate variants, including solubility, biological stability (related to clearance by the kidney (see Example 3)) as well as pharmaceutical efficacy, which is necessary for the variant to effectively exert activity of decreasing plasma glucagon concentration, The specification describes biological half-time related to "clearance by the kidney" of the unmodified exendin-4 peptide (see Example 3,and Figures 5 and 6). However, the specification fails to teach the same with regard to the polymer-modified exendin and analog thereof.

Because the claimed method involves highly variant polymer-modified exendin conjugates, outcome of administering the composition comprising the polymer-modified exendin to a subject whose in vivo glucagon level is needed to be is unpredictable.

Absence of the guidance in the specification as to which ones (the variants) would or would not have been a priori active or inactive would not enable the skilled artisan to practice what the invention discloses. The specification does not describe the consequence of the variants, i.e., the polymer-modified exendin or analog thereof and their therapeutic use, and fails to describe the common attributes or characteristics that identify any polymer-exendin conjugates.

The specification is, thus, insufficient to enable skilled artisan to practice the invention as broadly claimed without an undue amount of experimentation.

Application has disclosed only the exendin-4 and PEG-exendin modification. Note that exendin belongs to a group of peptide hormones in relation the glucagon family, including exendin 1, 2, 3 and 4, wherein helospectin is exendin-1; helodermin is exendin-2. Applicants are not in a possession of any polymer-modified exendins (1-4) and analog thereof.
The skilled artisan cannot envision all the contemplated polymer-modified-exendin possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of the variants, i.e., any polymer-modified exendin molecule, any exendin analog and any polymer-modified exendin analog and to describe their glucagonostatic activity,

and fails to provide written description regarding their therapeutic use for treating disease states, e.g., glucagonoma and type II diabetes. Thus, Applicant was not in a possession of making and using the polymer-modified exendin compounds for treating disorders associated with abnormally high plasma glucagon (see "Summary of the invention at page 1, lines 31-33). *See University of California v. Eli Lilly and co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In consideration of the issued stated *supra*, the amount and level of experimentation needed is undue.

Claim Rejection - 35 U.S.C. 112, the second paragraph

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "therapeutic lowering of plasma glucagon". Because the specification does not define the phrase 'therapeutic lowering", such the recitation is unclear as to whether or not therapeutic lowering refers to in vivo lowering process or a drug treatment associated process. Also, claim is indefinite as to the recitation "exendin analog" because the specification provides no definition of it and because the recitation is unclear regarding whether or not the recitation encompasses exendin agonist, antagonist or/and chemically modified exendin, e.g., PEG-conjugated exendin molecule. In addition, claim 1 recites "polymer-modified exendin" for

which the specification does not describe; the recitation is not apparent regarding whether or not the recitation includes any polymer, e.g., polynucleotide, polypeptide, lipid or any organic polymer, e.g., polyethylene glycol (PEG). Further, claim 1 is unclear in the recitation "polymer-modified exendin analog"; what is a difference between the polymer-modified exendin and the polymer-modified exendin analog, and between the exendin analog and the polymer-modified exendin? As for as "modified" is concerned, to what is the modification compared (*e.g.*, modification of exendin-4, or modification of an exendin analog that has been chemically modified)? and, to what kind of modification does the claim refer? (*note that modification can be divided into 4 categories: physical, chemical, enzymatic and genetic modification, wherein, physical modification refers to, e.g., multimerization and aggregation; enzymatic modification refers to, e.g., proteolytic cleavage of exendin peptide; chemical modification refers to, e.g., an amino acid side-chain modification; and genetic modification regards, e.g., mutagenesis of exendin peptide*). See also claims 4, 9-10 and 15-16. the dependent claims are also rejected.

Claim 7 is unclear as to the recitation "exendin or exendin agonist"; in biochemistry and pharmacology, agonist refers to a drug that binds to a receptor on a cell to produce a physiologic reaction typical of a naturally occurring substance. Thus, the recitation is indefinite regarding whether or not exendin agonist refers to a molecule naturally occurring in mammal or human (note that mammal and human do not naturally produce exendin) or includes exendin *per se*. Additionally, claim 7 recites "said polymer-modified exendin …comprises an exendin or exendin analog is linked to one or more polyethylene glycol (PEG) polymers"; the recitation is unclear as to (*i*) whether or not "modified" refer to any chemical modification rather than PEG modification (*i.e.*, PEGylation), i.e., whether or not prior to PEG modification the exendin

peptide has been modified; and (*ii*) whether or not the PEGylated exendin is further subject to second PEG modification. The dependent claims are also rejected.

Claim 14 recites "exendin" and "exendin analog". There is insufficient antecedent basis for this limitation in the claim 9 from which claim 14 depends because claim 9 only recites the polymer-modified exendin and polymer-modified exendin analog (note that the polymer-modified exendin or the polymer-modified exendin analog is different molecule from exendin and exendin analog, respectively).

Response to the rejection under 35 USC 112, the second paragraph

The response filed 21 November 2002 discusses the issue regarding the recitation "exendin and exendin agonist" and asserts that the recitation is not indefinite as one of skill in the art would be appraised of the scope of the claim (see page 1, section IV, the second paragraph). The applicant's argument is found unpersuasive. The recitation is indefinite because the specification has not described a difference between exendin and exendin agonist, and see also the statement of the above rejection.

Claim Rejections - 35 USC §102

Claims 1-5, 10-13, 15, 17 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Eng, J. (US Pat. No. 5424286).

Eng teaches that an insulinotropic peptide, e.g., glucagon-like insulinotropic peptide (GLIP) significantly lowers the plasma concentrations of insulin and glucagon (see column 1,

lines 59-62), and explicitly teaches that, exendin-4 is an insulinotropic agent (see column 2, lines 44-46). Thus, lowering plasma glucagon in a subject is inherent in the patent. The Eng's patent also teaches treatment of patient suffering from non-insulin dependent diabetes mellitus (NIDDM) who has increase in plasma concentration of glucagon by administering to the subject (patient) effective insulinotropic amount of exendin-4 (SEQ ID NO:2) (see column 1, lines 59-64, claim 6, and Figures 3and 5), which meets the limitation set forth in claims 1 and 10 as to a method of lowering plasma glucagon in a subject comprising identifying a subject in need of lowering plasma glucagon and administering exendin peptide. Eng teaches exendin-4 of SEQ ID NO:2 (see column 4, line 33) that consists of 39 amino acids, which meets the limitation of claim 1, i.e., exendin sequence is more than 30 amino acid residues in length. Thus, the Eng's patent anticipates claims 1 and 10 of the instant application.

Since necrolytic migratory erythema is a sympton of glucagonoma (see Bloom, S. R. *et al.* (1987) *Am. J. Med.* 82, (suppl 5B) 25-36), which is associated with elevated plasma glucagon level due to the islet cells over-production of glucagon, and since inhibition of glucagon secretion results in decreasing glucagon level in a patient, ability of exendin-4 to decrease plasma glucagon is applicable to treatment of glucagonoma. Thus, claims 2 and 3 are anticipated by Eng's patent disclosure.

Since the exendin sequence of SEQ ID NO:2 of Eng's patent reads on SEQ ID NO: 47 of the current aplication (note that residue 40 is –OH group as indicated in the filed seuqence-listing of this application), Eng anticipates claims 4-5, 15 and 17 of the instant application. The sequence of SEQ ID NO:2 of Eng' patent meeets all limitation set forth in claim 20 of the current application; thus, claim 20 is anticipated by the patent. Note that position 27 of SEQ ID NO: 48

of the application claim 20 is Lys-Asn (see page 45, line 13, wherein "X_1" is position 27), which corresponds to residues 27-28 of SEQ ID NO:2 of Eng's patent (see Table 1).

Eng teaches exendin-4 and methods for the treatment of diabetes mellitus and the prevention of hyperglycemia using exendin-4 and derivatives (see abstract), as applied to claims 11-12 of the current application. Because non-insulin dependent diabetes mellitus, *i.e.*, type II diabetes, is marked by hyperglycemia which is prevented by administration of exendin-4 peptide (see column 2, lines 37-40), claim 13 is anticipated by the patent as well.

Thus, Eng' patent anticipates claims 1-6, 10-13, 15, 17 and 20 of the current application.

Claims 1-3 and 10-13 are rejected under 35 U.S.C. 102(a) as being anticipated by the reference (*Marketletter*, Published on 24 August 1998, newly cited).

The reference teaches a process of using exendin-4 to inhibit glucagon secretion and clinically treat Type II diabetes patient (an identified subject) for the treatment. The reference teaching meets the limitation of claims 1 and 10 of the instant application. Necrolytic migratory erythema is a sympton of glucagonoma which is associated with elevated plasma glucagon level, due to the islet cells over-production of glucagon. The reference teaches that exendin-4 inhibits glucagon secretion thereby lower glucagon level; thus, the reference anticipates claims 2 and 3 as well.

The reference teaches clinial trials for using exendin-4, as applied to claim 6 of the instant applivcation. Also, the reference teaches single doess of subcutanous exendin-4 for

treating patient with type 2 diabetes, which meets the limitations set forth in claims 11-13 of the current application.

Response to the rejection under 35 USC 102(b) and 102(a)

The response filed 29 April 2003 asserts that Eng does not teach all of the limitation of the claims as (i) Eng does not teach or suggest the ability of exendin to lower glucagon levels but in reference to the ability of GLIP to lower meal-related increases in plasma concentration of glucagon; and (ii) Eng fails to suggest the benefits of exendin role in therapeutic lowering of glucagon levels (see page 13, the second paragraph). The applicants' argument is found not persuasive. Eng teaches insulinotropic agent significantly decreases plasma concentration of glucagon and exendin-4 is a potent insulinotropic agent (see column 2, line 51), and teaches that the use of an effective amount of exendin-4 as a treatment for diabetes mellitus has the advantage of being more potent than other insulinotropic peptides and greatly reducing the risk of hypoglycemic side effects (see column 2, lines 49-60). Thus, exendin lowering plasma glucagon in a subject is inherent in the Eng's patent. See also the above rejection.

Also, the response argues that Eng does not teach or suggests the lowering of glucagon levels in a subject suffering from glucagonoma by administering an exendin (see page 13, the third paragraph). The applicants' argument is unpersuasive because of the reasons set forth in the statement supra. Applicants are reminded of that necrolytic migratory erythema is a sympton of glucagonoma, and glucagonoma is associated with elevated plasma glucagon level. Because exendin-4 is a more potent agent than GLIP in insulinotropic effect, e.g., lowering plasma glucagon as taught by Eng (see column 2, lines 49-51), the method comprising administering

exendin-4 to a subject (see claim 4 of Eng patent) is thus applicable to treating glucagonoma including treatment of glucagonoma caused disorder, e.g., necrolytic migratory erythema.

In response to the jection under 35 USC 102 (a), the applicants commend that the Markeletter reference is not qualifie for the prior art because the reference does not meets the critira "by another" in view of that Amylin Pharmaceuticls, Inc is the assignee of the present application (see page 14). 35 USC 102 (a) states that Applicant's disclosure of his or her own work within the year before the application filing date cannot be used against him or her under 35 U.S.C. 102(a). *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). The common assignee does not establish commmon inventor(s) in this case. Thus, the rejectiom is maitained.

The response argues that the Marketletter reference contains no indication that exendin-4 would act in a manner similar to that of GLP-1 with regard to glucagonostatic actiity (see page 14, the second paragraph). The apploicat's argument is not persuasive becasue the reference teaches that exendin-4 shares many of the propertie of GLP-1 and offers an obvious advantage over GLP-1 in that exendin-4 has much longer biological duration (i.e., considerablely higher *in vivo* half-time). Thus, exendin-4 is a clinical candidate (see the first two lines) for treating disease, e.g., type II diabetes and inhibiting glucagon secretion.

Claim Rejections - 35 USC §103

Claims 1-17 and 19-20 are rejected under 35 U.S.C. 103(a) as being obvious over Eng J. (US Pat. No. 5424286) taken with the reference (*Marketletter*, 24 August 1998, newly cited), Drucker, D. J. (US Pat. No. 6051557), Frank, D. *et al.* (US Pat. No. 4179337) and Beeley, N. *et al.* (WO 9830231).

Eng teaches that an insulinotropic peptide, e.g., glucagon-like insulinotropic peptide-1 (GLP-1), significantly lowers the plasma concentrations of insulin and glucagon (see column 1, lines 59-62), and explicitly teaches that, exendin-4 is an insulinotropic agent (see column 2, lines 44-46). Thus, lowering plasma glucagon in a subject is inherent in the patent. The Eng's patent also teaches treatment of patient suffering from non-insulin dependent diabetes mellitus (NIDDM) who has abnormally elevated concentration of glucagon *via* administering to the subject (patient) effective insulinotropic amount of exendin-4 (SEQ ID NO:2) (see column 1, lines 59-64, claim 6, and Figures 3and 5), which meets the limitation set forth in claims 1 and 10 as to a method of lowering plasma glucagon in a subject comprising identifying a subject in need of lowering plasma glucagon and administering exendin peptide. Eng teaches exendin-4 of SEQ ID NO:2 (see column 4, line 33) consisting of 39 amino acids, which meets the limitation of claim 1, i.e., exendin sequence is more than 30 amino acid residues in length. The Eng's teaching is applied to claims 1, 4, 9-10, 14 and 16-17 of the instant application.

Since necrolytic migratory erythema is a sympton of glucagonoma, which is associated with elevated plasma glucagon level, and since inhibition of glucagon secretion would result in decreasing glucagon level in a patient, ability of exendin-4 to decrease plasma glucagon is applicable to treatment of glucagonoma. The Eng's teaching therefore meets the limitation set forth in the application claims 2 and 3.

The exendin sequence of SEQ ID NO:2 of Eng's patent reads on SEQ ID NO: 47 of the current aplication (note that residue 40 is –OH group as indicated in the filed seuqence listing of this application), which meets the limitation of claims 4-5, 15, 17 and 19 of the instant application. Also, the sequence of SEQ ID NO:2 of Eng' patent meeets all limitation set forth in

claim 20 of the current application. Note that position 27 of SEQ ID NO: 48 of the application claim 20 is Lys-Asn (see page 45, line 13, wherein "X_1" is position 27), which corresponds to residues 27-28 of SEQ ID NO:2 of Eng's patent (see Table 1).

Eng teaches exendin-4 and methods for the treatment of diabetes mellitus and the prevention of hyperglycemia using exendin-4 and derivatives (see abstract), as applied to claims 11-12 of the current application. Type II diabetes is marked by hyperglycemia which can be prevented by administration of exendin-4 peptide (see column 2, lines 37-40), which meets the limitation of the application claim 13.

Thus, Eng' teaching is thus applied to 1-5, 9-17 and 19-20 of the current application.

The Marketletter reference teaches a process of using exendin-4 to inhibit glucagon secretion and clinial trials for using exendin-4 in treatment of Type II diabetes, as applied to claim 6 of the instant applivcation. Also, the reference teaches single doess of subcutanous exendin-4 for treating patient with type II diabetes. which meets the limitations set forth in claims 11-14 of the current application.

The Eng patent and the *Marketletter* reference do not, however, expressly teach conjugation of PEG polymer to exendin or exendin analogs.

Drucker *et al.* teach conjugate of PEG homopolymers to glucagon-related peptide (GLP), which is structurally and functionally related to exendin in order to enhance solubility of the peptide in aqueous solution, increase stability in storage, reduce immunogenicity, increase the peptide resistance to proteolytic degradation, and increase *in vivo* half life of the peptide (see column 19). Drucker *et al.* teach covalent linkage of peptide hormone to one or more polymers;

Of the polymers, PEG homopolymer is particularly preferred (see column 19, lines 26-28 and 44-45). The Drucker *et al.* teaching is applicable to the limitation of claims 1, 4, 7, 9-10 and 15-16 of the instant application.

Frank *et al.* teach that covalent conjugation of polypeptides and peptide hormone, *e.g.*, insulin to polyethylene glycol (PEG) having a molecular weight of 500 to 20,000 daltons (see claims 1 and 14-23 and columns 2-3), as applied to claim 8 of the instant application. Note that the Frank *et al.* reference has been incorporated by Drucker *et al.*

One of ordinary skill in the art would have combined the teachings of the above references to arrive at the current invention, because (i) Eng teaches substitution of exendin-4 for GLP-1 which has therapeutic effect on decreasing plasma glucagon, (ii) the *Marketletter* teaches treatment of a patient (human) suffering from a disease state associated with abnormally elevated glucagon level by administering exendin-4 (GLP-1 substitute) to the patient, and (iii) Beely and Frank teach the conjugation of PEG to exendin peptide, and teach the biological favorableness of the PEG-conjugated exendin (see below). When combined, there would have been the following advantages: (***a***) PEG-conjugated exendin has enhanced solubility in aqueous solution, increased stability in storage, reduced immunogenicity, increased the peptide resistance to proteolytic degradation, and prolonged *in vivo* half life (see column 19), as taught by Drucker *et al.*; (***b***) exendin-4 has much longer in vivo duration than cognate GLP-1 which half-time is too short to make a commercially-useful product, suggesting the exendin is a candidate for clinical use for treating disease states, e.g., type II diabetes that associates with elevated glucagon levels, as taught by the *Marketletter* reference; and (*c*) PEG having a MW 500-20,000 daltons offers a

physiological active non-immunogenic as well as water-soluble polypeptide composition, as taught by Frank *et al.* (see abstract and Claims 1 and 14-23).

Given the above motivation, one of ordinary skill in the art would have combined the above reference teachings, and would have resulted in use of the PEG-exendin-4 compounds for lowering plasma glucagon, and thereby treating disorders or diseases associated with abnormally high plasma glucagon, e.g., glucagonoma and type II diabetes with exendin-4 or active PEG-conjugated exendin-4 as claimed in the current application (but NOT *a polymer*-modified exendin or polymer-modified exendin *analogs*).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483.

The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703-308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel W. Liu, Ph.D.

June 23, 2003

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER